Childhood arrestees: neural correlates of antisocial and psychopathic development

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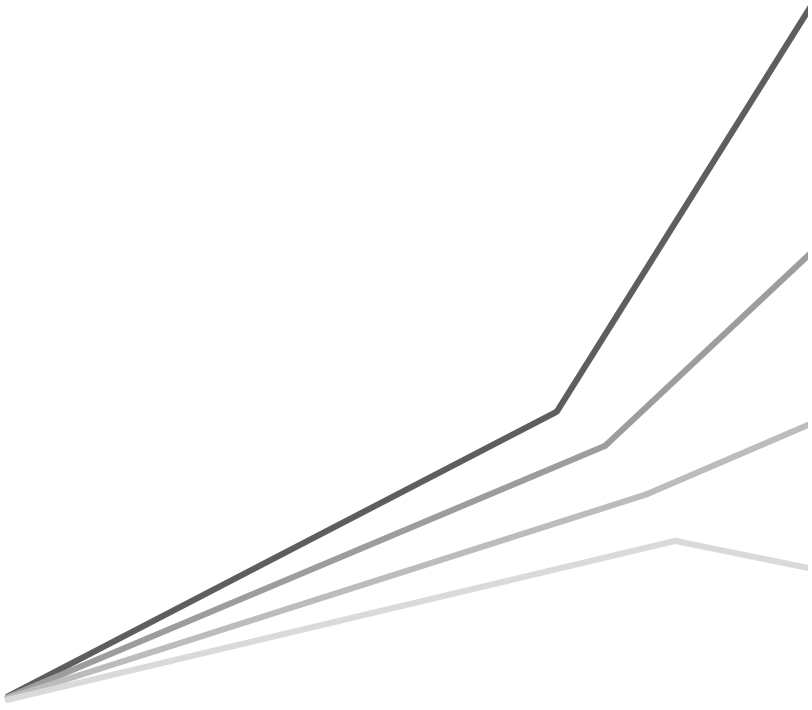
2017

document version
Publisher's PDF, also known as Version of record



10 Summary and general discussion

Summary

This thesis aimed to investigate the neural correlates of high-risk developmental patterns in childhood arrestees followed up in late adolescence. Particular emphasis was directed towards phenotypic specification, using both longitudinal (i.e. persistence) and cross-sectional (i.e. psychopathic traits) subtyping approaches. Below, we summarize the main findings.

Part 1 – Functional neural correlates of DBD persistence and psychopathic traits in late adolescence

In our fMRI fear conditioning study, we found that both persistent and desistent DBD youth showed enhanced responses of the fear neurocircuitry during acquisition (**chapter 2**) and extinction (**chapter 3**) of conditioned fear responses when compared to healthy controls. These differences were mediated by the presence of impulsive-irresponsible psychopathic traits, which were positively associated with differential fear responses. In a multidimensional model investigating the independent effect of each psychopathic trait dimension while controlling for all other psychopathic trait dimensions, impulsive-irresponsible traits and grandiose-manipulative traits were positively associated with fear responses, whereas callous-unemotional traits were negatively associated. Consequently, we performed a computational modeling study (**chapter 4**) which revealed that both callous-unemotional and impulsive-irresponsible traits were uniquely positively associated with uncertainty about contingencies, while only impulsive-irresponsible traits were positively associated with uncertainty about the likelihood of contingency changes, which may partly explain the previous findings. In our fMRI reward and loss processing study (**chapter 5**) DBD persisters showed lower responses in the ventral striatum during reward outcomes and higher responses in the amygdala during loss outcomes. Callous-unemotional traits were related to lower responses in the amygdala during reward outcomes.

Part 2 – Structural and connectivity correlates of psychopathic traits in late adolescence

In our voxel-based morphometry study (**chapter 6**), we found that grey matter concentration in the amygdala was negatively associated with callous-unemotional traits, but positively with conduct disorder symptoms. A significant interaction between the severity of antisocial behavior and callous-unemotional traits was detected in the prediction of grey matter volume in the insula, indicating that only subjects low on antisocial behavior showed a significant positive association between callous-unemotional traits and grey matter insula volume. With respect to structural connectivity (**chapter 7**), positive associations between FA and grandiose-manipulative traits were detected in a wide range of white matter tracts, while positive associations between FA and callous-unemotional traits were only significant in the corpus callosum and the corticospinal tract. In addition, there were indications for distinct pathophysiological mechanisms, as indicated by differential associations with radial and axial diffusivity. Finally, the analyses on resting-state functional connectivity (**chapter 8**) revealed that callous-unemotional traits were related to atypical connectivity of the default mode network, while impulsive-irresponsible traits were significantly associated with frontoparietal network connectivity.

Part 3 – Childhood maltreatment and reward processing in late adolescence

In our fMRI study on the association between childhood maltreatment and reward and loss processing in late adolescence (**chapter 9**), we found evidence for distinct associations between maltreatment subtypes and reward processing, such that physical abuse was associated with higher ventral striatum (VS) responses during reward and loss anticipation, whereas physical neglect was associated with lower VS responses during reward anticipation and higher VS responses during reward outcome. Sexual abuse was associated with higher VS responsiveness during loss anticipation and higher parietal responses during loss outcome.

Discussion

Taken together, the studies in this thesis provide evidence for substantial neurobiological heterogeneity in early-onset antisocial juveniles with neurobiological differences between DBD persisters and desisters and differential associations with psychopathic trait dimensions.

Persisters versus desisters

With respect to the subgroup analyses, these findings support the notion that (1) fear hyperresponsiveness is involved in the development of antisocial behavior, but (2) does not necessarily lead to persistence of such behavior; whereas (3) monetary incentive processing deficits do seem to specifically increase the risk of persistence. Although persistence was not uniquely predicted by fear acquisition or extinction deficits, DBD persisters did show a pattern of atypical fear responsiveness, which is likely to reflect deficient inhibition of fear responses, as deficits were more pronounced during extinction than late acquisition (Quirk & Gehlert, 2003). Similar to what has been proposed for anxious persistent offenders (Frick et al., 2006; Hodgins et al., 2009), fear hyperresponsiveness in our sample was (at least partly) explained by the presence of impulsive-irresponsible traits. It seems, therefore, plausible that fear conditioning deficits may put youth at risk of persistent antisocial development, but only in the presence of other risk factors a full-blown disorder emerges, whereas protective factors may lead to desistence. While social factors have been shown to interact with fearfulness in the prediction of persistent antisocial development (Kochanska et al., 2007), additional biological risk factors may also increase the risk of persistent antisocial behavior. In this respect, we have shown that aberrant reward and loss processing is present in the persistent DBD subgroup, and we have proposed several explanations for these findings. First, lower responses to rewarding outcomes may lead to excessive sensation seeking – including delinquency or substance abuse – in order to restore dopamine levels to homeostasis (Zuckerman & Neeb, 1979). Second, as adequate function of the ventral striatum is a prerequisite for reinforcement learning (Li et al., 2011), its hyporesponsiveness may explain some of the operant conditioning deficits that have been reported in antisocial youth (e.g. Newman & Kosson, 1986; Newman et al., 1990; Budhani & Blair, 2005). This explanation may be important because most of the current treatments for antisocial behavior involve some form of behavior therapy using the principles of reinforcement learning. In addition, there are indications that youths high on callous-unemotional traits only benefit from behavior therapy when they additionally use dopaminergic psychostimulants (Waschbusch et al.,

2007). Third, loss hyperresponsiveness may reflect some form of threat hypervigilance – similar to what has been reported in relation to our fear conditioning findings. Importantly, however, we did not find evidence for the assertion that the anticipation of either monetary loss or an aversive electric stimulus differentiated between persisters and desisters, suggesting that it is the processing of loss outcome (rather than anticipation) that is altered specifically in persisters. An anonymous reviewer of our work has suggested that higher responses during loss outcome may also indicate higher saliency of external feedback, which may relate to deficiencies in internal error processing, which have been reported in adult psychopaths (von Borries et al., 2010). Further research is needed to test these hypotheses, and should include computational modeling to assess whether this pattern of lower reactivity to positive outcomes and higher reactivity to negative outcomes reflects more basic dysfunctions, such as aberrant prediction error coding (White et al., 2013c).

Psychopathic trait dimensions

Dimensional analyses with psychopathic traits as independent variables suggested that impulsive-irresponsible traits partly explained fear hyperresponsiveness, while callous-unemotional traits were associated with fear hyporesponsiveness and atypical reward processing, suggesting their potential for phenotyping antisocial youth in relevant ways. However, we observed several other – and more general – associations between neural aberrations and psychopathic traits: first, limbic neurocircuitry function and grey matter concentration were generally negatively associated with callous-unemotional traits (**chapters 2, 3, 5 and 6**), but positively with impulsive-irresponsible and antisocial traits (**chapters 2, 3, and 5**). With respect to impulsive-irresponsible traits, we suggested that such associations may arise as a consequence of deficient inhibitory processes, given the presence of specific extinction deficits (**chapter 3**) and the observed associations with the frontoparietal network connectivity and amygdala hyperconnectivity within the salience network (**chapter 8**). Alternatively, exaggerated limbic responsiveness to aversive information may arise as a consequence of aberrant uncertainty coding. In **chapter 4**, impulsive-irresponsible traits were associated with higher subjective uncertainty about contingencies, as well as with an overestimation of change likelihood uncertainty. We speculate that these features may interact with other latent variables such as negative bias (which was not estimated in the current study), leading to a sensitization of the fear neurocircuitry (cf. Herry et al., 2007; Whalen, 2007) and explaining why individuals high on these traits show higher fear conditioning (**chapter 2**) and fail to extinguish conditioned fear responses (**chapter 3**). Callous-unemotional traits, on the other hand, may be associated with reduced fear learning (**chapter 2**) due to a selective deficit in contingency uncertainty estimation (**chapter 4**). However, these traits were associated with hyperconnectivity of the frontopolar cortex in the default mode network (**chapter 8**), and with higher structural connectivity in the corpus callosum and corticospinal tract (**chapter 7**). We have argued that these findings may carry relevance for moral reasoning processes, for instance by allowing higher cognitive control to guide utilitarian moral decision-making styles, as reported in some psychopathic individuals (Koenigs et al., 2012; although see Cima et al., 2010). Such atypical connectivity patterns in relation to callous-unemotional traits in our sample could be the consequence of a primary amygdala dysfunction during moral decision making (Glenn et al., 2009), as has been proposed by Blair (2013). However, alternative explanations for these findings – i.e. associations of functional differences in higher-order cognitive networks with callous-

unemotional traits, which are commonly associated with more basic limbic dysfunctions – are possible. First, limbic hyporeactivity may be secondary to higher recruitment of inhibitory brain regions: preliminary evidence for this suggestion is provided by both neuropsychological (Newman et al., 2010; Baskin-Sommers et al., 2011) and neuroimaging studies (Larson et al., 2013), although others have criticized this position (Blair, 2010; White et al., 2012a). Second, equifinality may be invoked to explain these findings: multiple neural mechanisms (i.e. primary limbic hyporeactivity and primary higher recruitment of inhibitory regions; Larson et al., 2013) may manifest phenotypically as callous-unemotional traits. Given other indications for within-trait heterogeneity of callous-unemotional (Cecil et al., 2013), this suggestion warrants further research. Grandiose-manipulative traits, although traditionally grouped in PCL-R 'Factor 1' with callous-unemotional traits, showed distinct associations with neural function and connectivity: unique variance attributable to grandiose-manipulative traits was positively associated with amygdala function during fear acquisition (**chapter 2**) and with widespread higher structural connectivity (**chapter 7**). The amygdala hyperreactivity finding should be considered preliminary, given evidence to the contrary in adults engaged in negative picture viewing (Carré et al., 2013). However, we would like to argue that – also here – within-trait heterogeneity may moderate research findings (cf. Baskin-Sommers et al., 2014). Notably, grandiose-manipulative traits have been estimated to share about one quarter to half of their variance with callous-unemotional traits in the general population (Andershed et al., 2002a) and offenders (Neumann et al., 2007), respectively, and are similar to such traits in their association with empathy deficits (Watson et al., 1984; Fan et al., 2011, although see Baskin-Sommers et al., 2014). However, they are not necessarily the consequence of a primary empathy deficit: such deficits in the closely related narcissism construct may rather be due to primitive defensive responses, initiated in order to maintain the inflated sense of self characteristic of this condition and to repress the negative affects associated with past traumatic experiences and (Modell, 1975; Kernberg, 1985; Cohen, 1985). Indeed, narcissism has been preferentially associated with reactive rather than proactive aggressive (Bukowski et al., 2009), and both reactive aggression (Van Bokhoven et al., 2005) and narcissistic traits (Edelstein et al., 2010; Reinhard et al., 2012, although see Loney et al., 2006; Feilhauer et al., 2013) have been associated with higher cortisol responsiveness, indicating hyperreactivity of stress neurocircuitry – contrarily to what has been reported in callous-unemotional traits (Loney et al., 2006). In summary, it can be concluded that in terms of limbic reactivity, dimensional analyses may enhance specificity but are still substantially hampered by equifinality, most notably in the form of a distinction between a primary empathic deficit and an acquired deficit, resembling what has been previously termed 'primary and secondary' psychopathy (Karpman, 1941). Further research is therefore needed to disentangle the interactions between trauma and psychopathic traits in the prediction of neural responsiveness. Finally, we have argued that the widespread associations between grandiose-manipulative traits and hyperconnectivity is likely to reflect early (psychosocial) maturation, as argued by Berns and colleagues (Berns et al., 2009) with respect to hyperconnectivity and risk-taking in adolescence. However, structural hyperconnectivity has also been related to adolescent cannabis abuse and schizophrenia (Peters et al., 2009). Although no associations with cannabis use were found in the current study, we did not include a valid measure for psychotic symptoms in the current study. Further investigation of the relation between the current findings and psychotic symptoms is

warranted, given the increased risk for schizophreniform outcomes in our sample (Kim-Cohen et al., 2003).

Heterogeneity

It may be clear from the previous paragraphs that the neuropsychological frameworks described in the introduction of this thesis are too simplistic to account for the neurobiological variance in adolescents and adults with antisocial behavior, and may each apply to specific subpopulations. With respect to fearlessness, some evidence was found for its association with callous-unemotional traits (**chapter 2 and 3**) although this has been argued to reflect an epiphenomenon of the empathic amygdala deficit (cf. Blair, 2006). The absence of behavioral decision-making estimates in our own study precludes conclusions about the functional relevance of aberrant reward processing in the ventral striatum (**chapter 5**) for the reward dominance and model of antisocial development. However, we suggest that it would be overly simplistic to suggest that reward hypersensitivity is the main factor driving antisocial decision-making strategies, given the range of findings in reward processing studies in antisocial juveniles and the range of potential explanations provided for their association, including sensation seeking (Zuckerman & Neeb, 1979), reward dominance (Gorenstein & Newman, 1980), deficient reinforcement learning (Sagvolden et al., 2005), higher delay discounting (Hariri et al., 2006) and hypersensitivity to the rewarding effects of substance abuse (Hommer et al., 2011). As such, there seems to be a significant but complex relation between motivational processes and persistent antisocial development.

The role of childhood maltreatment

We have shown that childhood maltreatment contributes to a wide range of aberrations in regional brain function during reward and loss processing, which varied as a function of maltreatment subtypes. These motivational aberrations are likely to provide the neurobiological embedding for the vulnerability to a range of antisocial and non-antisocial negative mental health outcomes and warrant further research of their mediating role in such outcomes, as well as their potential for use in clinical practice, including prevention and intervention efforts.

Clinical implications

Although the nature of the current thesis does not allow firm conclusions about clinical practice, several preliminary suggestions will be made here. First, this thesis provides abundant evidence for neurobiological heterogeneity in antisocial juveniles and their developmental pathways, and confirms that at least one subgroup of persistent antisocial juveniles is characterized by a pattern of brain function that is best described as 'hyperreactive'. These findings should inspire clinicians to differentiate between subtypes of antisocial juveniles, because they are likely to respond differently to treatment (e.g. Waschbusch et al., 2007; Hawes et al., 2014). While further research is required to design optimized interventions for subgroups differing in their neurobiological makeup, we speculate that differentiating between children with high versus low threat reactivity may be relevant with regard to (1) differential parenting approaches, e.g. adjusting the level of

confrontation to a child's intrinsic reactivity (see Dadds & Rhodes, 2008, for an excellent discussion of this topic) and (2) differential effects of pharmaceuticals used in antisocial juveniles for treating co-morbid ADHD, which are known to influence fear conditioning (e.g. atomoxetine: Davis & Gould, 2007; methylphenidate: Abraham et al., 2012).

Second, as persistent antisocial juveniles in this sample were characterized by aberrant reward and loss processing, interventions aimed at the dopaminergic system, and motivational processes in general, also seem to be indicated and warrant further study. For example, there is preliminary evidence for the effectiveness of methylphenidate in enhancing the effectiveness of behavioral treatment in callous-unemotional antisocial juveniles (Waschbusch et al., 2007), which may be due to low dopaminergic reactivity in this specific subgroup (see chapter 3). Our findings again suggest that interventions aimed at the motivational system may be moderated not only by phenotypic variables (i.e. psychopathic traits), but also by exposure to childhood maltreatment. While neurobiological variation as a function of phenotype in late adolescence warrants a differentiated intervention approach, the association of reward sensitivity with childhood maltreatment exposure suggests that earlier interventions may be needed. Such interventions may not only include primary prevention and early detection of family violence at the societal level, but also environmental enrichment programs which have been shown to reduce antisocial outcomes in the general population (Raine et al., 2003b) and may do so in at-risk samples.

Phenotypically, neurobiological differences within antisocial juveniles are likely to be captured best by a multidimensional operationalization of psychopathic traits, a notion that is clearly at odds with the simplistic notion of adequate versus 'limited prosocial emotions' embraced by DSM-5. Again, large studies investigating treatment effectiveness and prognosis in subgroups of antisocial juveniles differentiated by these dimensions are needed: several suggestions in this respect are provided below.

Future research

While it is clear that a lot has still to be learned about the neurobiology of the complicated multidimensional construct of antisocial development, several strands of research deserve specific attention. First, there is a pressing need to assess whether treatment effectiveness of antisocial juveniles differs as a function of specific neurobiological (and phenotypic) characteristics, and whether optimizing treatment allocation enhances outcome in these youth. Second, several types of specific interventions warrant investigation: we suggest that it may be promising to combine CBT with pharmacological interventions targeting the dopaminergic system (e.g. methylphenidate, dexamphetamine) in youth presenting with reward-related aberrations, i.e. not restricting the use of such agents to youth presenting with a formal diagnosis of ADHD. In addition, there are several pharmacological interventions targeting the extinction deficits seen in post-traumatic stress disorder (e.g. D-cycloserine, propanolol, yohimbine) that deserve investigation of their effectiveness in treating antisocial individuals. Finally, in order to enhance our understanding of the neural underpinnings of antisocial development, neuroimaging studies should (1) use computational modeling to comply with what we know about how the brain actually codes information, (2) investigate how regional brain dysfunction influences brain function on a network level, e.g. using graph analysis and (3) investigate neural development of participants longitudinally.